

PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY

First Meeting Of The

DIRECTING COUNCIL

**Dacca, East Pakistan
February 1962**

DC 1/14

DC 1/14

February 26, 1962.

REMARKS OF THE DIRECTOR OF THE CRL

The marble tablet at the entrance of the Pakistan-SEATO Cholera Research Laboratory commemorates its dedication on December 5th, 1960. Those present at the dedication will remember that the Bacteriological Laboratory was already working.

Those who had visions of a great immediate flowering of scientific work during the past year have been disappointed but in the long range perspective of the study and prevention of cholera, the situation is far more favourable today than could have been predicted at the time of the dedication.

This is not the place to repeat information presented in other documents of the Directing Council, but it is surely not amiss to call attention to a number of factors which together justify considerable optimism regarding the future of the Pakistan-SEATO Cholera Research Laboratory:

- 1) Epidemiology now has, through the development of a special medium by the Bacteriologic Section of the CRL, a tool through which the distribution of cholera may be charted routinely and systematically throughout the year in endemic areas. This is particularly important in the determination of those areas which are the permanent seed beds of cholera infection.
- 2) The CRL, a year ago had neither plans nor resources for the study of the relationship of water supply to cholera; today the CRL has, a rather complete water laboratory which needs only a qualified Water Biologist to go forward with studies to determine why the permanent seed beds of cholera in the world are in the delta areas along the shores of the Bay of Bengal.
- 3) The widespread penetration of cholera into the Western Pacific in 1961 has been most timely in emphasizing the continuing importance

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of cholera as an international health problem. Just as the invasion of Thailand by cholera in 1958 - 1959 stimulated the creation of the CRL, so has the invasion of the Western Pacific forced the recognition of the need for a cholera study center, with a broad program covering all aspects of the disease, its prevention and eradication.

- 4) The 1962 visit of Dr. Joseph Smadel, the Chairman of the NIH Cholera Advisory Committee with three Committee Members and two Consultants, has resulted in the acceptance of much broader plans for the program of the CRL. The Committee has decided that the 1961 experience with cholera in the Western Pacific "emphasizes the need for the intensification of work on all aspects of this disease by individual scientists and by national and international groups. Furthermore, the rolling front of cholera in the Western Pacific demands that the CRL assume some of the obligations implied under its SEATO banner."

The Committee commented on the long range objective that should be brought to the attention of this Directing Council, the staff of the laboratory and the supporting groups and expressed the hope that its comments might become incorporated into the philosophy of the CRL. These comments are:

- "1. It is the opinion of the Committee that the problem of cholera is of such broad significance to world health that any activity short of one which brings the techniques of science to bear directly and importantly on the many problems of the disease is shortsighted and inadequate.
- "2. The CRL has already established itself as a key factor in the apparatus that will be required to eradicate the disease. Support for the CRL is imperative in obtaining funds, physical facilities, and the high level scientific staff it requires to contribute its share to the accomplishment of the enormous tasks ahead.
- "3. Consequently, it is recommended that the staff of the CRL, continue their planning with less regard to the funds which have been available up to the present than to the importance of the task they address themselves to."

In considering the significance of this statement, it must be remembered that Dr. Smadel and the NIH Cholera Advisory Committee, have been largely responsible for planning the USA participation in the CRL.

- 5) Fortunately, the legal framework in which the Pakistan-SEATO Cholera Research Laboratory functions has been revised in such a way that the

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CRL can readily assume and discharge the responsibilities of a regional Center for all phases of the study and prevention of cholera in collaboration with other institutions and with governments.

The Original Agreement of October 14, 1960 (DC 1/1, Annex II) creating the CRL was cast in the mould of the bilateral aid agreement of limited scope and duration. The Revised Agreement of December 30, 1961 (DC 1/1 Annex IV) makes possible a broad international program for the study and prevention of cholera, through the CRL as an autonomous agency in which interested countries may participate both financially and in the determination of policy and program. This autonomous agency can readily become the mechanism for international assistance all to countries with cholera or threatened by cholera. As an autonomous agency the Pakistan-SEATO Cholera Research Laboratory can receive grants and operate freely so long as it maintains the confidence of contributing nations and organizations. The prototype of the CRL, the Institute of Nutrition of Central America and Panama (INCAP) has maintained the confidence of grantors and contributing organizations and has made scientific and public health contributions in tropical nutrition many times greater than could have been done with its basic budget derived from member States.

- 6) The immediate basic financial needs of the CRL for the remainder of Fiscal 1962 and for Fiscal 1963 have been provided for through the provisions of the Revised Agreement (DC 1/1, Annex IV) through the Grant Agreement between the NIH and the CRL (DC 1/1, Annex V) and through a recent addition through AID, of \$150000 to the SEATO Cholera Research Fund.

The First Meeting of the Directing Council of the CRL is not, as many first meetings are, preliminary to the creation of the corresponding agency. The CRL exists legally, physically and financially, with money in the bank and provision for basic financial needs guaranteed to June 30, 1963. The Directing Council then does not face many of the responsibilities inherent in Directing Councils, since the Revised Agreement of December 30, 1961 (DC 1/1, Annex IV) and the NIH/CRL Grant Agreement of January 25, 1962 (DC 1/1, Annex V) together settle many immediate problems.

It has been possible to call this meeting without the previous distribution of the draft agenda and pertinent documents, since there are no serious matters requiring decision at this time; rather should this meeting be considered an informational and organizational one at which the Members of the Council will come to know the CRL, and its special autonomous status, and make provision for the fundamental operation of the CRL until the next meeting at which budget and program decisions will be necessary.

PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY

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February 5, 1962.

ANTECEDENTS OF THE PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY 1959 - 1961.

The SEATO Cholera Research Program

In the years immediately following World War II, cholera was reported over a wide area; from Japan far to the north-east in the Pacific and westward to Egypt in North Africa both far from the traditional endemic seedbeds of the disease in the delta regions facing on the Bay of Bengal. During the partition of the Indian sub-continent cholera was a serious problem in West Pakistan, but apparently disappeared for a number of years after 1949. During the early 1950's reports of cholera were very largely limited to East Pakistan and to India.

This period of relative quiet for cholera was broken abruptly in 1958 by the reappearance of cholera in West Pakistan and in Thailand. The disease spread rapidly from the capital, Bangkok, to some 39 provinces of Thailand. As a direct result of this epidemic the delegate of Thailand to the 1959 SEATO Conference in Wellington, New Zealand, proposed a SEATO Cholera Research Program.

The SEATO Cholera Research Program was initiated through an agreement between the United States Government and the Secretary-General of SEATO on May 29, 1959, (ANNEX I). By the terms of this agreement the United States Government contributed \$400,000 to be spent by the National Institutes of Health of the Public Health Service of the Department of Health, Education and Welfare of the United States in the study of cholera in collaboration with institutes in Asia.

The Pakistan-SEATO Cholera Research Laboratory - 1960

Following the rapid spread of cholera in Thailand in 1958 and early 1959, the disease declined rapidly and it was obvious, at the time of the visit of the NIH Cholera Advisory Committee (August 1959), that long term studies of cholera could not be carried out in Bangkok. The Institute of Public Health of East Pakistan at Dacca was chosen as headquarters for cholera studies because of the permanent endemicity of cholera in the delta region of the Ganges and Brahmaputra Rivers.

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On October 14, 1960, the Governments of Pakistan and of the United States signed an agreement creating the Pakistan-SEATO Cholera Research Laboratory as part of the SEATO Cholera Research Program (ANNEX II).

Some laboratory equipment and technical staff had been provided even before the signing of the Agreement with the result that the Bacteriological Section began to function in November some weeks before the official inauguration of the CRL, on December 5, 1960, during the SEATO Conference on Cholera (December 5-8, 1960).

The SEATO Cholera Conference was held as part of the SEATO Cholera Research Program for the purpose of bringing together from other countries up to date information on cholera research needed for the orientation of continuing cholera studies. Unfortunately, the workers of India were not represented.

Among the accomplishments of 1960 one may list (a) the negotiation and signature of the Agreement of October 14, 1960, (b) the selection and training in the United States during a four months' period of a Pakistan scientist to serve as Chief of the Bacteriological Laboratory, (c) the installation of the Bacteriological Laboratory, (d) the SEATO Cholera Conference in Dacca 5-8, 1960 and (e) the contribution of £10,000 by the United Kingdom for the purchase of equipment and supplies for the Cholera Research Laboratory.

The Pakistan-SEATO Cholera Research Laboratory - 1961

Very early in 1961 it became apparent that the Agreement of October 14, 1960, establishing the Pakistan-SEATO Cholera Research Laboratory was not adapted to the development of a flexible expanding program in cholera research. Inadequate provision for budget and staff and the absence of administrative unity created a difficult situation.

Some months elapsed in an unsuccessful attempt to adapt the October 14, 1960, Agreement to the needs of a flexible research effort.

On May 10, 1961, the Director of the CRL proposed, to the Governments of Pakistan and of the United States, a revision of the CRL Agreement providing for the transformation of the CRL into an autonomous international agency. Realizing that some months would be required for the negotiation of the revised agreement, the Special Advisory Committee appointed by the Governor of East Pakistan in April 1961, to facilitate the development of the Cholera Research Laboratory, recommended, on May 29th, that the CRL operate, during the interim period, under the general agreement between the International Cooperation Administration of the United States and the Government of Pakistan. Both governments accepted this recommendation and an interim agreement, modifying that of October 14, 1960, was signed on July 28, and became operative late in August (ANNEX III). The Interim Agreement continued in operation until December 31, 1961. As had been foreseen, the negotiation of the Revised Agreement was slow,

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due to the fact that various agencies of each Government had to participate in the study of the Director's proposed Revision. Each Government made modifications which had to be negotiated in due course. The Revised Agreement creating the Pakistan-SEATO Cholera Research Laboratory as an autonomous international agency was signed on December 30, 1961, (ANNEX IV). This agreement provides that the CRL operate under the immediate scientific direction of the National Institutes of Health and under the general direction of a Directing Council, composed of representatives of each of the participating SEATO nations, of the Secretary General of SEATO and of the Director of the National Institutes of Health.*

During the year 1961, preliminary arrangements were made for a research grant from the National Institutes of Health, through which the United States commitment to the financing of the CRL for Fiscal Years 1962 and 1963 might be guaranteed and additional provision made for expansion of scientific and field studies of the CRL.

On January 25, 1962, an agreement was signed by the Director of the National Institutes of Health and the Director of the CRL providing for a research grant applicable to operations during the Calendar Years 1962 and 1963, (ANNEX V).

Among the accomplishments of 1961, the negotiation with the Governments of Pakistan and of the United States of the Revised Agreement of December 30, 1961, creating an autonomous agency which can become multilateral and regional in its operation, stands at the top of the list.

Other highly significant developments were :

a.) The development and field demonstration of special culture media for the cholera vibrio, adapted to field diagnosis, and to the routine collection and forwarding for examination by post of diagnostic material from otherwise inaccessible outbreaks;

b.) The installation of a functioning water analysis laboratory with equipment and trained Pakistani technicians on loan from AID, and the initiation of studies of tank and tube well waters;

* The prototype of this autonomous agency is to be found in the Institute of Nutrition of Central America and Panama (INCAP) with its headquarters in Guatemala City. In the case of (INCAP), the scientific and administrative direction is in the hands of the Pan-American Health Organization under the general government of a Directing Council composed of representatives of the six participating nations and of the Director of the Pan-American Sanitary Bureau. The original INCAP Agreement was written in 1946 and the Institute has been functioning very successfully in its chosen field of tropical nutrition since September of 1949

c.) The receipt and beginning installation of considerable amounts of scientific equipment from the United Kingdom and from the United States, for clinical, biochemical, physiological and therapeutic research on cholera patients;

d.) The addition of two highly qualified research scientists to the staff of the CRL from the staff of the National Institutes of Health;

e.) Serving as host to a group of three persons from the scientific staff of the Naval Medical Research Unit of the United States at Taipeh, Taiwan, for some weeks during which studies were made on the effect of diarrhoeal diseases on the functioning of the so-called sodium pump in cases at the Mitford Hospital;

f.) Bacteriological and epidemiological observations of cases of cholera in and around Dacca during the post monsoon period.

Annexes to DC 1/1

- I SEATO/USA AGREEMENT of May 29, 1959.
- II Pakistan-SEATO Cholera Research Laboratory Agreement of October 14, 1960.
- III Cholera Research Laboratory Interim Agreement of July 28, 1961.
- IV Cholera Research Laboratory Revised Agreement of December 30, 1961.
- V Research Grant Agreement between the National Institutes of Health and the Cholera Research Laboratory of January 25, 1962.

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SCOPE OF THE PROGRAM OF THE PAKISTAN-SEATO CHOLERA RESEARCH LABORATORY

The program of the Pakistan-SEATO Cholera Research Laboratory as outlined in the Revised Agreement of December 30th 1961 (ANNEX IV DC 1/1) is a broad one, with provision for collaboration with all interested nations and with other agencies.

The following significant paragraphs occur in the Revised Agreement:

"The modern approach to the prevention of communicable diseases in this age of jet transportation must be through eradication of the permanent seed beds of infection. The great historic seed bed of cholera includes parts of East Pakistan. The broad objective of the CRL is the development, evaluation and demonstration of measures of prevention and eventual eradication of cholera.

The CRL is established at the Institute of Public Health, Mahakhali, Dacca, East Pakistan. The Bacteriology Section has been operative for some months; additional Sections of Epidemiology, Physiological Chemistry, Water Analysis, Clinical Observation and Field Demonstrations are being developed.

The activities of the CRL necessarily cover all phases of cholera investigations and prevention. Attaining the immediate objective, i.e., the elucidation of the epidemiology of cholera in East Pakistan with the identification of those factors which permit cholera to remain endemic, decade after decade, depends on the improvement and standardization of bacteriological and immunological methods. As the epidemiological studies proceed, the effects of various means for preventing cholera will be studied. Among these are the effects (1) of intensive vaccination of selected population groups with different types of vaccine and (2) of the provision of potable water to discourage the drinking of tank and ditch waters. Studies will be made of the abnormal physiology of cholera cases in a search for a better system of treatment.

The CRL is to be capable of serving as the base for regional anti-cholera operations; it is intended that the studies and observations in East Pakistan will be supplemented by research based on both laboratory and field work in other cholera-infected countries. The CRL is a centre where visiting scientists and public health officials with special interests in and knowledge of cholera may come for firsthand contact with the problem. It is also a place where scientists and health administrators from other countries may be trained in methods for the study and prevention of cholera.

The activities of the CRL in East Pakistan will be coordinated to the maximum extent possible with the programs of the Health Services and of Public Health Engineering of the GOEP; in West Pakistan similar coordination with the Provincial authorities will occur should occasion arise for studies there; full advantage will be taken also of the opportunity for collaboration with projects sponsored by the Public Health Division of the AID Mission to Pakistan.

There is no SEATO cholera problem distinct from the cholera problem of the non-SEATO nations of the region and the final solution to the problem must come through a consolidated regional effort. Every effort is to be made to interest all cholera-infected nations and all countries threatened with cholera, and the corresponding Regional Offices of the World Health Organization, in the solution of the cholera problem.

Free interchange of information and direct collaboration wherever possible will be arranged with investigators and health authorities of nations and with the World Health Organization and with its Regional Offices.

Private agencies will be encouraged to support special cholera research and prevention study projects administered by the CRL."

A further outline of the objectives of the program of the CRL supported by the Research Grant Agreement with the NIH of January 25 1962 (annex V, DC 1/1) is worded as follows:

"Objectives and Description of Work to be performed

1. Objectives: To develop, improve, and demonstrate measures for the prevention and eventual eradication of cholera.

2. Description of Research Plan: The epidemiology of cholera in East Pakistan, a highly endemic area for this disease, will be investigated intensively, and will be studied elsewhere as opportunities occur. The ecology of the cholera vibrio, insofar as it may exist in water or other media apart from the human host, will be studied. Means for preventing and controlling cholera will be tested; these will include studies on intensive vaccination in selected areas and observations on the effect of the provision of potable water by the health authorities in other areas. Clinical studies directed toward a better understanding of the host-parasite relationship in acute cholera will be undertaken and, based on information obtained there, improved methods of prevention and treatment will be sought."

It is obvious that the CRL is not now ready to immediately undertake the broad program outlined above. The need for such a program has been emphasized during the months which have passed since this program was drafted. The unexpected spread of cholera to Macan, Hongkong, Communist China and the Philippines during the last half of 1961 found the CRL unprepared to render assistance or to take advantage of the opportunity for study of cholera epidemics in non-endemic areas.

The Directing Council may desire to take note of the need for execution of a broad cholera program as the DC studies the programs and budgets for future years.

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SCIENTIFIC PROGRAM OF THE PAKISTAN SEATO-CHOLERA RESEARCH LABORATORY.

The broad outline of the scientific program of the CRL, as established in the pertinent agreements (Annexes IV & V, DC 1/1), has been set forth in Document DC 1/4. The present document gives specific plans as formulated to date.

The essential facts regarding the occurrence of cholera are relatively simple. Cholera results from intestinal infection with Vibrio cholerae. It is spread through fecal contamination of food and drinking water, particularly the latter. The cholera organism does not form spores, and dies rapidly on drying, but may survive for some days, or possibly weeks, in a favourable moist environment. The organism multiplies extensively in the gastrointestinal tract, where it may persist for some weeks during convalescence. Long term chronic carriers are unknown.

Frank cholera cases are characterized by an extraordinary diarrhea which produces excessive dehydration; dehydration so severe as to cause death in many cases. Cholera, apart from dehydration, is seemingly very mild; rehydration with parenteral fluids is strikingly effective in reducing mortality to a very low figure. Rehydration, however, is of limited use in the field, because of the large amounts of sterile saline required and the necessity for careful control of the amount of saline given.

Although it is recognized that the eradication of cholera will come through preventive rather than therapeutic methods, the CRL is to open a small ward where the pathogenesis and abnormal physiology of this disease may be studied, the development of immunity and persistence of the carrier state observed, and the simplification of therapy attempted.

Some observers of outbreaks of cholera have seen that the disease tends to affect principally and, in many cases be limited to, the lower

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economic social group, have come to believe that factors other than insanitary conditions may influence individual susceptibility to a clinical attack of the disease. If nutritional status, pre-existing disease of the digestive system, or some other host factor be important in determining susceptibility, clues may be obtained by comparing cholera patients with unaffected persons from the same areas and walks of life. Such a comparison requires more laboratory tests and clinical observations than are commonly employed; the CRL ward has much more equipment and requires a considerably greater staff than are essential to a curative service. Observation on humans will be supplemented at times by studies in which laboratory animals are used.

The cholera problem will eventually be solved when effective economical methods of prevention have been developed and applied to the permanent endemic foci of infection. Epidemiologic studies of cholera, in the past, have been carried out almost entirely during epidemics. But a proper understanding of the mechanism by which cholera persists year after year in the delta areas of the Ganges and Brahmaputra Rivers can be had only after the endemic foci of infection have been demarcated and the mechanism by which V. cholerae survives, during the interepidemic period, has been determined.

Bacteriologic confirmation of the diagnosis of cholera on a province-wide basis has become possible through the development, at the CRL, of new media for the cultivation of V. cholerae from body fluids, domestic water supplies and foods. (DC 1/6). The CRL in collaboration with the Health Services of the Government of East Pakistan proposes to utilize these media in the development of a province-wide program for the routine, systematic, bacteriologic diagnosis of cholera in asymptomatic carriers, in sporadic cases, in small outbreaks and in epidemics on a year round basis in order to demarcate endemic foci within the endemic area, to observe the routes of epidemic spread, and to identify areas which are most suitable for a variety of special investigations. Material for diagnosis will be collected routinely by the health officers from outbreaks which come to their attention. Beyond the health officer, at the village or school district level, the CRL will have local representatives to forward diagnostic material systematically by mail whenever cases of severe diarrhea occur in their respective villages or districts.

The CRL cannot undertake the diagnosis of all cholera cases in East Pakistan nor does it desire to do so. In studying methods of cholera prevention, determination of the number of cases has secondary importance to that of outlining the temporal and geographical distribution of the disease. As it becomes possible to follow the occurrence of cholera through bacteriologic diagnosis of material collected and processed in a routine systematic way, studies will be planned to determine the influence of the mass cholera vaccination program, and of the programs for the installation

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of tube wells and sanitary latrines.

Until the bacteriologic diagnostic service of the CRL has become well established, routine cholera mortality and morbidity statistics of the Government of East Pakistan, now under study, will be utilized to the maximum possible extent for selecting the areas most suitable for programs planned by the CRL.

The importance of water as a vehicle for infection was demonstrated by Snow in 1849, but the specific way in which the water supplies of endemic areas contribute to the permanency of endemicity has never been identified. Studies recently conducted in Dacca revealed that the pH in water in tanks increased during the course of bright sunny days from neutral to a strongly alkaline reaction (DC 1/14). It has been suggested that this favors survival of the V. cholerae through the inhibition or destruction of other competing organisms which cannot withstand as strongly alkaline environments as can the cholera vibrios. The CRL possesses facilities and materials for conducting chemical and bacteriological examinations on sources of water used in East Pakistan for drinking, for personal and for domestic purposes. Water used by cholera infected and controlled households for drinking and domestic purposes will be examined routinely as a part of investigation of cholera outbreaks.

Special year round studies will be undertaken to determine the possible relationship of the tank to the persistence of endemic cholera. The study of survival of the cholera vibrio under simulated natural conditions of the tank will also be explored at the CRL. This program will latter be expanded to consider the influence of other components of the environment; e.g. soil, on the survival of pathogenic vibrios.

Studies particularly concerned with immunity and differences in exposure to infection will be conducted to determine the characteristics of individuals who suffered an attack of cholera and which distinguish them from others, who escaped infection or become asymptomatic carriers. This will be included in the epidemiological investigations of outbreaks of the disease.

Evaluation of methods for the prevention of cholera will be undertaken and will include special studies of immunity, immunization with vaccines containing killed vibrio cholera organisms and the general improvement of sanitation through the installation of tube wells for a safe water supply and of bored hole latrines for sanitary sewage disposal.

Studies of immunity and the antibody response of indigenous persons following immunization can be initiated with the least amount of delay, particularly in military recruits and prisoners. Both of these groups are subject to discipline which simplifies the collection of serum specimens. The CRL is not at the present prepared to perform serologic examinations

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but will submit these specimens to other laboratories for study.

No controlled field trials have yet been conducted to demonstrate the efficacy of any vaccines which are now employed for the prevention of cholera. The CRL will be developing plans for the controlled field trial of several vaccines. Two of those recently have been found to vary widely in their ability to prevent death of mice inoculated intraperitoneally with V. cholerae. This observation cannot be assumed to have any relationship to the value of the vaccines for man until further evidence has accumulated during the course of controlled vaccine trials in human populations. Other vaccines being considered for study include the vaccine produced at the Institute of Public Health of East Pakistan and a new vaccine which the CRL has been requested to test by the Bureau of Laboratories of the Government of Pakistan.

The Public Health Engineering Department of the Government of East Pakistan has, as one of its goal during the Second Five Year Plan, the installation of one tube well for every four hundred people in the province. The importance of the tube well program as a measure for controlling cholera arises directly because contaminated water is an important vehicle of infection and indirectly as a requirement for maintaining a high standard of personal hygiene to prevent transmission through contact. Whether or not the ratio of wells to population which is present goal will prove adequate for interrupting transmission of cholera remains to be determined. The CRL proposes in collaboration with the Public Health Engineering Department to study the use of tube well in the control of cholera. Specific points of interest concerned the ratio of wells to population which will provide sufficient readily available potable water for personal and household uses. Since cholera is unevenly throughout the province it would appear that tube wells should be concentrated in some areas, particularly those where the disease is endemic. Determination of the needs in this regard must await more precise demarcation of such endemic centers. Other points to be considered will be the most suitable location of tube wells within the villages and factors which govern the utilization by the people of contaminated water rather than potable tube well water.

As another means for improving the general standard of sanitation the program for the installation of bored hole latrines has been initiated by the government. The program has made little progress primarily because the bored hole latrine has not been accepted by the people. The CRL is interested in undertaking only a pilot study of methods for successfully introducing this sanitary measure in a selected area.

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